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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,786	10/17/2003	Henry R. Costantino	1733.2025-003	9558

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EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,786	COSTANTINO ET AL.	
	Examiner	Art Unit	
	Anand U Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31-35* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/04 & 11/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 2-22 in the reply filed on November 10, 2004 is acknowledged. The traversal is on the ground(s) that Group I and III are related as genus/species, and that a search of claims 4, 13, and 18 will result in the search of claim 31. Applicant states that Groups I and II are related as a combination/subcombination. Applicants state that it is untrue that the method of Group IV can be practiced with a materially different product. This is not found persuasive for the restriction between the products and method of use inventions. The method of treating a patient suffering from Type 2 diabetes (Group IV) can be performed by a materially different pharmaceutical composition, such as a composition comprising 5-({3,5-bis[N-(6-sulfonaphthyl) carbamoyl]phenyl}-carbonylamino)naphthalene-2-sulfonic acid (see U.S. Patent 6,600,069, claims 1, 10, and 18). The composition claims will be rejoined as single invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 36-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on November 10, 2004. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of

right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Claim 1 is a linking claim, which is being examined with the elected invention of Group I. Claims 1-35 are currently pending and are under examination.

Priority

4. This application claims priority under 35 U.S.C. 119(e) to U.S. Provisional application 60/419,388. The priority date is October 17, 2002.

Information Disclosure Statement

5. The information disclosure statements (IDSs) submitted on July 27, 2004 and November 10, 2004 have been considered by the examiner.

Claim Objections

6. Claim 11 is objected to because of the following informality: The word "ins" appears to be intended to be "is". Appropriate correction is required.

7. Claim 30 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 5-17, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berstein et al. (U.S. Patent 6,749,866 B2) in view of Lee and Timasheff (Journal of Biological Chemistry Vol. 256, No. 14, pp. 7193-7201 (1981)).

Berstein et al. discloses a composition for the modulated release of a biologically active pharamaceutical agent, comprising a biocompatible and biodegradable polymeric matrix, an

effective amount of a biologically active pharmaceutical agent, including proteins, and a metal cation component for modulating the release of the biologically active agent from the polymeric matrix, wherein the metal cation is selected from the group consisting of magnesium hydroxide, magnesium carbonate, calcium carbonate, zinc carbonate, magnesium acetate, zinc acetate, magnesium chloride, zinc chloride, magnesium sulfate, zinc sulfate, magnesium citrate, and zinc citrate (see U.S. Patent '866, claim 1). Berstein et al. teach the stabilization of a protein pharmaceutical agent during the formation of a controlled release polymer matrix composition due to the presence of a polyion chelating the protein. Berstein et al. describe the controlled release of human growth hormone over a 60 day time period (see Example XII). The polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s polyanhydrides, polyorthoesters, polyetheresters, polycaprolactone, polyesteramides, blends and copolymers thereof (see U.S. Patent '866, claim 2). The biologically active agent is present from about 0.01% (w/w) to about 50% (w/w/) of the composition (see U.S. Patent '866, claim 1). Berstein et al. does not disclose the composition comprising a sugar.

Lee and Timasheff disclose the stabilization of proteins in the presence of sucrose. Circular dichroism and protein absorbance measurements at different temperatures were performed with varying sucrose concentrations to see the effects of sucrose on protein stabilization. The sucrose is preferentially excluded from the protein domain, thereby increasing the apparent activation energy of the unfolding process for the protein and thus stabilizing the protein (see Figure 2, Table 2, and Discussion section).

One would have been motivated to form a sustained release composition comprising a biocompatible polymer, a biologically active polypeptide, and a metal cation, such as magnesium

acetate as disclosed by Berstein et al. along with a sugar such as sucrose as disclosed by Lee and Timasheff, because of the stabilization of the biologically active polypeptide with both metal cations, and sugar during the formation of a sustained release microparticle composition. Therefore, it would have been obvious to the person having ordinary skill in the art to manufacture a sustained release composition comprising a biologically active polypeptide, a biocompatible polymer, a salting-out salt, such as magnesium acetate, and a sugar, such as sucrose (current application, claims 1, 2, 5-17, and 19-22).

10. Claims 3, 4, 18, and 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berstein et al. (U.S. Patent 6,749,866 B2) in view of Lee and Timasheff (Journal of Biological Chemistry Vol. 256, No. 14, pp. 7193-7201 (1981)) as applied to claims 1, 2, 5-17, and 19-22 above, and further in view of Taylor, K. et al. (Diabetes 51 (suppl. 2):85 Jun 2002).

Taylor, K. et al. disclose the use of synthetic exendin-4 for the treatment of patients with type 2 diabetes. Synthetic exendin-4 was given as an infusion over the course of 10 consecutive days to four patients with type 2 diabetes inadequately controlled with metformin and/or diet. The results of exendin-4 administration demonstrated the effectiveness of lower glucose. Taylor, K. et al. also suggest the motivation for a long-acting release formulation of synthetic exendin-4 that may provide sustained glycemic control.

One would have been motivated to use the sustained release microparticle of Berstein et al. with the exendin-4 disclosed by Taylor, K. et al. to treat patients with type 2 diabetes inadequately controlled with metformin and/or diet. Therefore, it would have been obvious to the person having ordinary skill in the art to manufacture a sustained release composition

comprising a glucoregulatory peptide such as exendin-4 with various pharmaceutical excipients, including salts, such as magnesium acetate, and sugars, such as sucrose (current application, claims 1-22, and 31-35).

11. Claims 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berstein et al. (U.S. Patent 6,749,866 B2) in view of Lee and Timasheff (Journal of Biological Chemistry Vol. 256, No. 14, pp. 7193-7201 (1981)) as applied to claims 1, 2, 5-17, and 19-22 above, and further in view of Silvestri et al. (U.S. Patent 5,126,147).

Silvestri et al. disclose a multiphasic sustained release delivery system for prolonged, controlled delivery of microencapsulated macromolecular bioactive agent, comprising a macromolecular bioactive agent of a biological origin encapsulated in microcapsules of bioerodible encapsulating polymer, which permits a sustained, multiphasic release of said macromolecular bioactive agent, and where the harmful effects of the released macromolecular bioactive agent are controlled by the synchronous release of an agent for symptomatic treatment of initial adverse reactions to the initial dose of the bioactive agent, wherein the agent for symptomatic treatment comprises a corticosteroid (see U.S. Patent '147, claims 1, 4, and 5). Silverstri et al. also disclose the state of the art of using different polymers to make heterogenous microspheres (see U.S. Patent '147, column 4, lines 10-13).

One would have been motivated to manufacture a sustained release composition further comprising a corticosteroid to reduce an initial adverse reaction upon administration of the bioactive agent. Therefore, it would have been obvious to the person having ordinary skill in the art to manufacture a sustained release composition comprising a biologically active polypeptide,

a biocompatible polymer, a salting-out salt, such as magnesium acetate, a sugar, such as sucrose, and a corticosteroid, wherein the corticosteroid is either coincorporated or separately incorporated into a biocompatible polymer (current application, claims 1, 2, 5-17, and 19-29).

12. Claims 1, 2, 5-17, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woiszwillo et al. (U.S. Patent 5,981,719) in view of Berstein et al. (U.S. 6,749,866 B2).

Woiszwillo et al. disclose microparticles formed by mixing a macromolecule with a polymer. The microparticles allows for the sustained release of macromolecule and polymer from the interior of the microparticles when placed in an appropriate aqueous medium. When preparing the microparticles containing protein, a protein stabilizer such as glycerol, fatty acids, sugars such as sucrose, ions such as zinc, sodium chloride, or any other protein stabilizers known to those skilled in the art may be added prior to the addition of the polymers during microparticle formation to minimize protein denaturation (see U.S. Patent '719, column 9, lines 3-8). Woiszwillo et al. disclose the formation of leuprolide acetate-containing sustained release microparticles. A 0.01 ml aliqout of a solution of 10-100 mg/ml leuprolide acetate in water (LHRH) was added to 0.168 ml of a 2-10% solution of dextran sulfate in water, and the solution was thoroughly mixed. A 0.856 ml aliquot of a solution containing 25% (weight/volume) polyethylene glycol, and 25% polyvinylpyrrolidone in 0.1M sodium acetate, pH 5.5 aqueous solution was mixed with the leuprolide/dextran solution. A 0.25 ml aliquot of a 20% solution of human serum albumin in water was then added to the solution. The solution was thoroughly mixed and placed in a water bath to form microparticles. The microparticles were composed of approximately 10% leuprolide acetate, 50% human serum albumin, 20% dextran sulfate, and

20% polyethylene glycol/polyvinylpyrrolidone. The release kinetics of leuprolide acetate-containing sustained release microparticles is shown on figure 8. (see U.S. Patent '719, Example 6, claims 1, 4, 7, 11, and 12, and Figure 8). Woiszwillo et al. does not disclose the use of a salting-out salt.

Berstein et al. discloses a composition for the modulated release of a biologically active pharamaceutical agent, comprising a biocompatible and biodegradable polymeric matrix, an effective amount of a biologically active pharmaceutical agent, including proteins, and a metal cation component for modulating the release of the biologically active agent from the polymeric matrix, wherein the metal cation is selected from the group consisting of magnesium hydroxide, magnesium carbonate, calcium carbonate, zinc carbonate, magnesium acetate, zinc acetate, magnesium chloride, zinc chloride, magnesium sulfate, zinc sulfate, magnesium citrate, and zinc citrate (see U.S. Patent '866, claim 1). Berstein et al. teach the stabilization of a protein pharmaceutical agent during the formation of a controlled release polymer matrix composition due to the presence of a polyion chelating the protein. Berstein et al. describe the controlled release of human growth hormone over a 60 day time period (see Example XII). The polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s polyanhydrides, polyorthoesters, polyetheresters, polycaprolactone, polyesteramides, blends and copolymers thereof (see U.S. Patent '866, claim 2). The biologically active agent is present from about 0.01% (w/w) to about 50% (w/w) of the composition (see U.S. Patent '866, claim 1).

One would have been motivated to form a sustained release composition comprising a biocompatible polymer, a biologically active polypeptide, and a metal cation, such as magnesium acetate as disclosed by Berstein et al. along with a sugar such as dextran sulfate as disclosed by

Woiszwillo et al., because of the stabilization of the biologically active polypeptide with both metal cations, and sugar during the formation of a sustained release microparticle composition. Therefore, it would have been obvious to the person having ordinary skill in the art to manufacture a sustained release composition comprising a biologically active polypeptide, a biocompatible polymer, a salting-out salt, such as magnesium acetate, and a sugar, such as sucrose (current application, claims 1, 2, 5-17, and 19-22).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 25, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER